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USE OF TRANSGENIC MICE FOR THE EFFICIENT ISOLATION OF NOVEL HUMAN MONOCLONAL

ANTIBODIES WITH NEUTRALIZING ACTIVITY AGAINST PRIMARY HIV-1 STRAINS AND NOVEL HIV-1

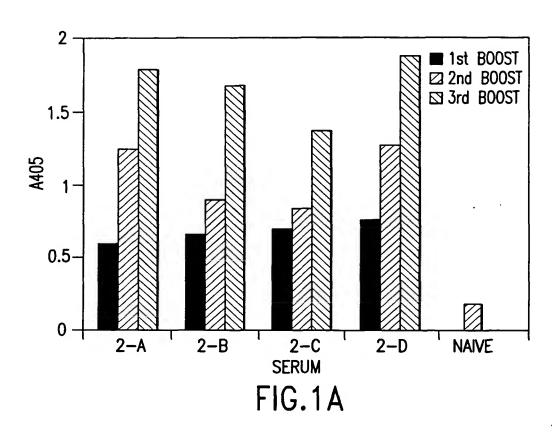
NEUTRALIZING ANTIBODIES

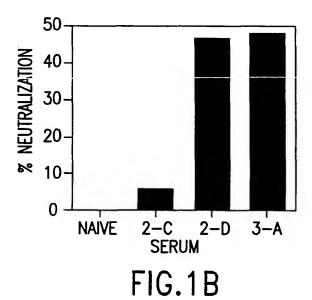
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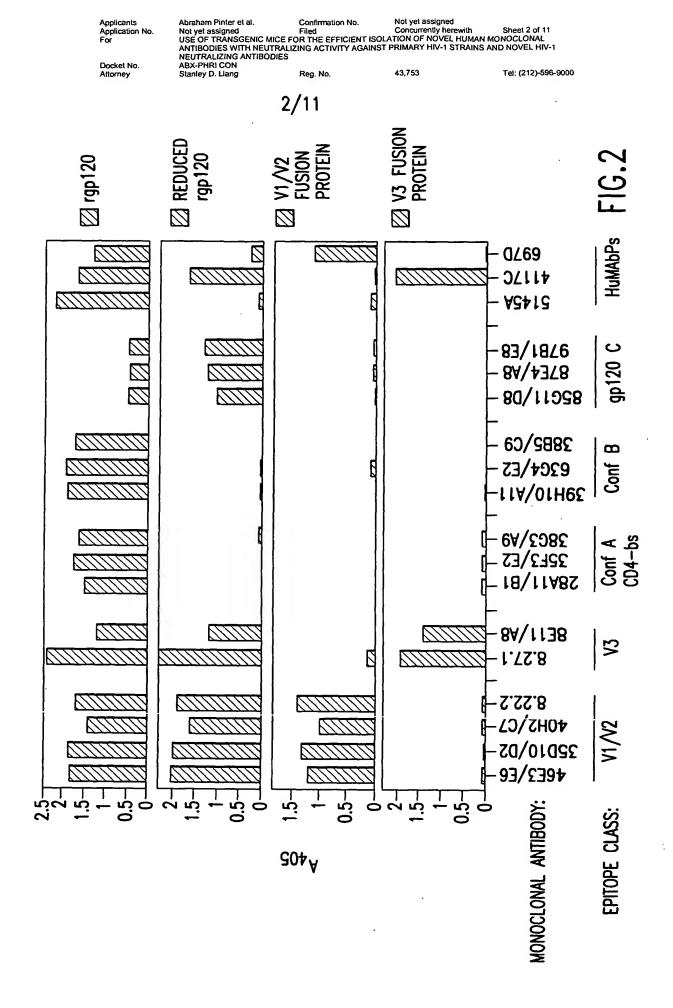
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Docket No. Attorney

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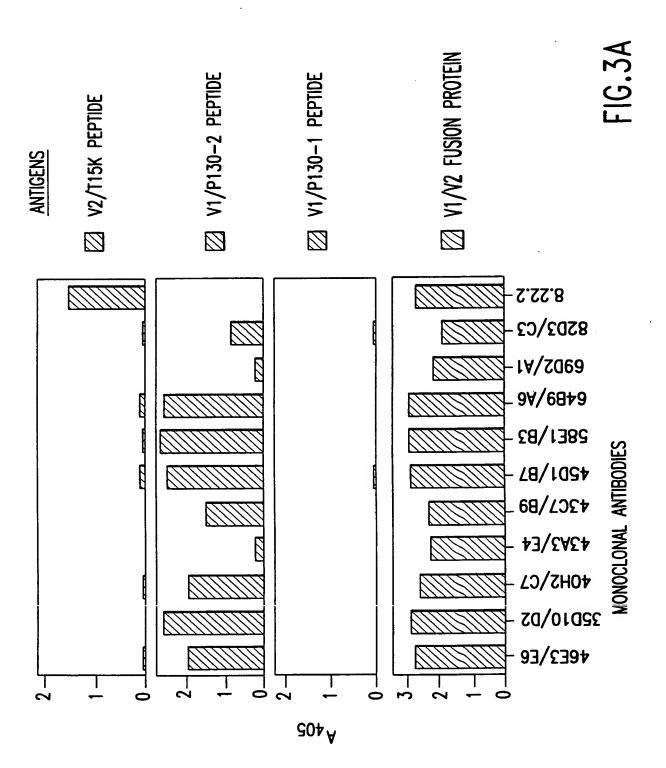
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USE OF TRANSGENIC MICE FOR THE EFFICIENT ISOLATION OF NOVEL HUMAN MONOCLONAL
ANTIBODIES WITH NEUTRALIZING ACTIVITY AGAINST PRIMARY HIV-1 STRAINS AND NOVEL HIV-1
NEUTRALIZING ANTIBODIES
ABX-PHRI CON
Stanley D. Liang
Reg. No.
43,753
Tel: (212)-596-5

Docket No. Attorney

Tel: (212)-596-9000





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NEUTRALIZING ANTIBODIES
ABX-PHRI CON
Stanley D. Liang
Reg. No.
43,753
Tel: (212)-596-5 Docket No. Tel: (212)-596-9000 Attorney :: **9** ;; SEQ 1D NO: SEQ 10 N SEQ 1D 1 SEQ 1D 1 LKPCVKLTPLCVTLHCTNL KNATNTKSSNWKEMDRGEIKNCSF KVTTSIRNKWQKEYALFYKLDVVPIDNDNTSY KLINCNTSVITQACPKVS RICHT STEM TTSIRDKVQKEYALFYK 72

NTKSSNWKEMD GEIK

P130-1 P130-2 T15K

STNL KNATNTKSSNW

CENTRAL

5

LEFT STEM

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ANTIBODIES WITH NEUTRALIZING ACTIVITY AGAINST PRIMARY HIV-1 STRAINS AND NOVEL HIV-1

NEUTRALIZING ANTIBODIES ABX-PHRI CON Stanley D. Liang

Docket No. Attorney

Reg. No.

43,753

Tel: (212)-596-9000

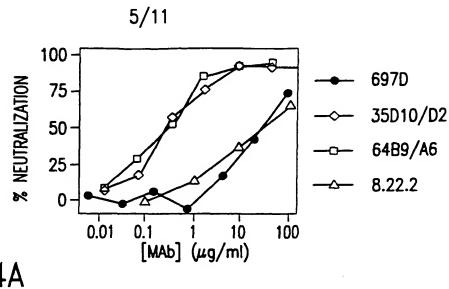


FIG.4A

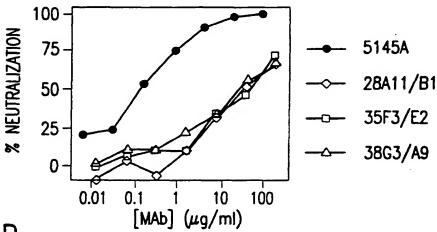
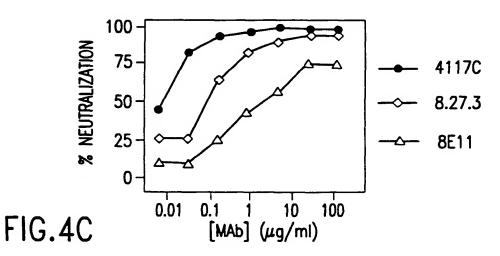


FIG.4B



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ANTIBODIES WITH NEUTRALIZING ACTIVITY AGAINST PRIMARY HIV-1 STRAINS AND NOVEL HIV-1

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ABX-PHRI CON

Stanley D. Liang

Reg. No.

43,753

Tel: (2121-596-6

Tel: (212)-596-9000

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COMPET	TING Mab	% INHIB	MON OF BIND	ING BY	BIOTINYLATED
EPITOPE	NAME	43A3/E4	35D10/D2	697D	sCD4
	35D10/D2	89	89	7	. 26
	40H2/C7	82	83	5	13
	43A3/E4	78	82	9	10
	43C7/B9	82	83	8	13
	45D1/B7	85	85	11	17 ·
V1 LINEAR	46E3/E6	86	86	9	-29
	58E1/B3	88	88	4	21
	64B9/A6	89	89	12	24
•	69D2/A1	58	65	12	37
	82D3/C3	52	56	11	-35
V2 LINEAR	8.22.2	1	1	84	-1
V2 CONF.	697D	3	-5	83	6
	SC258	9	21	45	0
V 3	8.27.3	9	24	11	9
CD4bs	5145A	0	11	-55	93

FIG. 5

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NEUTRALIZING ANTIBODIES
ABX-PHRI CON Docket No. Reg. No. Tel: (212)-596-9000 Attorney Stanley D. Liang 43,753 7/11 21-40 0.00 0.05 0.06 0.05 0.05 0.12 0.05 0.01 0.03 0.03 12 13 9999999 7 0.03 1.72 0.05 0.06 0.12 0.07 .22 0.07 SEQ SEQ SEQ YTTKNI IGTIRQAHCNI SRA 1-20 0.30 2.53 2.10 0.01 0.04 2.72 3.26 2.60 1.94 3.51 CTRPNNNTRKS I T I GPGRAF YA TGD I IGD I RQAHC CTRPSNNTRKS1H1GPGRAFYTTGE11GD1RQAHC CTRPNYNKRKR I H I GPGRAF Y T TKN I I GT I RQAHC TRPNYNKRKR I HIGPGRAFYTTKN I IGT I RQAH TRPNNNTRKS I R I QRGPGRAF VTTGK I GNMRQAH SYNTHETIC PEPTIDE 0.02 0.00 1.99 1.14 0.02 0.02 0.03 0.09 RIHIGPGRAFYTTKNI IGT 0.02 **=** SEQUENCE YNKRKR I H I ORGPGRAF Y T TKN I WN-IIB 0.29 3.36 0.08 0.06 0.05 0.13 0.07 0.95 1.60 1.57 3.11 CTRPNYNKRKR I HIGPGRAF Circular 1.79 2.00 0.88 0.99 0.94 1.11 1.60 2.84 1.82 2.51 inear 2.56 2.90 0.82 0.75 0.94 2.07 2.02 1.46 2.03 2.90 1.75 PND MN/IIIB MN 6-27 + QR HIV-11IIB (34 aa) JR-CSF Linear 2.56 0.98 0.87 2.03 2.20 1.49 1.54 2.96 1.84 FUSION PROTEIN JR-CSF (fusion protein) SOLATE JR-CSF **Zircular** (rqp120) 2.03 2.73 1.94 3.00 3.56 . 194 3.08 2.03 3.11 circular MN 11-30 MN 21-40 1-20 MN linear SF162 447-52D 8.27.3 **4117**C 4148D 838 1006 694 419 ¥ ₹ 皇 FIG. 6B FIG. 6A 0 ပ 8 ш GROUP XENOMOUSER HuMabPs Mabs

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% INHIBITION OF BINDING BY BIOTINYLATED

		% INT	IDITION OF DIN	DING DI DIC	TINILAILU
EPITOPE	COMPETING Mab	sCD4	CD4bs 38G3/A9	Conf-B 63G4/E2	gp120-C 97B1/E8
	38G3/A9	86	91	-29	ND
	35F3/E2	86	90	-22	ND
Conf A	55D5/F9	87	8 5	-18	ND
CD4bs	28A11/B1	82	ND	ND	. ND
	46D2/D5	62	ND	ND	ND
	67G6/C4	61	ND	ND	ND
	38B5/C9	5	-32	84	ND
	39H10/A11	0	-32	91	ND
	40D3/C11	9	-26	90	ND
	49B11/A1	12	-29	90	ND
	52G5/B9	19	-37	90	ND
Conf B	56C4/C8	17	-45	88	ND
	57H5/D7	32	-15	90	ND
	63G4/E2	27	-24	91	ND
	55E4/H1	13	-46	81	-35
	57B6/F1	-1	-23	56	-34
	65B12/C5	20	-22	40	-31
	85G11/D8*	14	-3	0	65
gp120 £	87E4/A8*	20	-11	-3	70
	97B1/E8*	20	-13	-1	71
CD4bs	5145A	93	. ND	ND	ND
V 3	4117C	30	ND	ND	ND

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		R5	CLADE	В	X4	CLADE	В	CLA	DE E 9/11
EPITOPE	Mab	SF162	BaL	JR-FL	MN	IIIB	SF2	93TH975	CM235
}	8.27.3	++	++	++	++	-	++	_	-
V3	6.7 8E11/A8 6.1	++ ++ ++	+ + +	+ + +	+ + +	- - -	- - -	- - -	- - -
V1 LINEAR	35D10/D2 40H2/C7 43A3/E4 43C7/B9 45D1/B7 46E3/E6 58E1/B3 64B9/A6 69D2/A1* 82D3/C3*	++ ++ ++ ++ ++ ++ ++ ++ ++	-	-	-	-	- - - - - -	- - - - - - -	- - - - - - - -
V2	8.22.2	++	++	++	_	-	-	_	-
Conf A CD4bs	28A11/B1 35F3/E2 38G3/A9 55D5/F9	++ ++ ++	+ ++ ++ ++	+ + + +	++ ++ ++ ++	++ ++ ++ ++	+ + + +	- - -	- - -
	46D2/D5	++	+	- [+	++	+	-	-
	67G6/C4*	+	-	-	-	_	-	_	-
	39H10/A11 63G4/E2	++	++	++	++	++	+ +	+++	+ +
Conf B	38B5/C9 52G5/B9 55E4/H1 49B11/A1 57H5/D7 40D3/C11	++ ++ ++ ++ ++	+ + + + + + +	+ + + + +	++ + + + + +	++ ++ ++ ++ +	- - - -	+ + + + +	- · · · · · · · · · · · · · · · · · · ·
	56C4/C8	++	- [+	+ -	++	- [+	**
	65B12/C5	+	+	- [+	+	-	-	-
	57B6F1	++	-	- [+	+	-	-	-
	97B1/E8*	+	+	+	+	+	+	-	-
gp120 C	87E4/A8*	+	+	+	+	+	-	-	-
	85G11/D8*	+	+	[+	_	_	-	-
CD4bs	5145a	++	++	+	'++	++	++	-	+

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FIG. 9

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ABX-PHRI CON
Stanley D. Liang
Reg. No.
43,753
Tel: (212)-596-5

Tel: (212)-596-9000

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-		10/11	
ЕРПОРЕ	Mab	CROSS-REACTIVITY	SF162 ND ₅₀
NEUTRALIZ	ING XENOMOUSE	R Mabs	
V1 Linear	35D10/D2 40H2/C7 43A3/E4 43C7/B9 45D1/B7 46E3/E6 58E1/B3 64B9/A6 69D2/A1* 82D3/C3*	SF162	0.27 1.9 3.2 1.4 1.9 0.30 0.55 0.29 4.5 1.2
V2 Linear	8.22.2	SF162 BaL JR-FL	48
V3 Linear	8E11/A8	SF162 Bal JR-FL MN	2.6
V3 Conf.	8.27.3	SF162 Bal JR-FL MN SF2	0.11
Conf. A CD4bs	28A11/B1 35F3/E2 38G3/A9 55D5/F9	SF162 Bal JR-FL MN IIIB SF2	35 60 31 37
NON-NEU	TRALIZING XENOM		
V3 Linear	6.1 6.7	SF162 Bal JR-FL MN	>50 >50
Conf. A CD4bs	46D2/D5 67G6/C4*	SF162 Bal MN IIIB SF2 SF162	>>200 >>200
	39H10/A11 63G4/E2	SF162 Bal JR-FL MN IIIB SF2 93TH975 CM235	>>200 >>200 >>200
Conf. B	38B5/C9 52G5/B9 55E4/H1 57H5/D7 40D3/C11 49B11/A1	SF162 Bol JR-FL MN IIIB 93TH975	>>200 >>200 >>200 >>200 >>200 >>200 >>200
	56C4/C8	SF162 JR-FL MN IIIB 93TH975	>>200
	57B6/F1	SF162 MN IIIB	>>200
	65B12/C5	SF162 Bal MN IIIB	>>200
an 100 C	85G11/D8*	SF162 Bal MN SF162 Bal JR-Fl MN IIIB	>>200 >>200
gp120 C	87E4/A8* 97B1/E8*	SF162 Bal JR-FL MN IIIB SF2	>>200
CONT	ROL HuMabPs	OF FOE BAL ON TE MIN ME GIE	.,,
CD4bs	51450	BROADLY REACTIVE	0.14
V2 Conf.	697D	BROADLY REACTIVE	80
V3 Linear	4117c	BROADLY REACTIVE	0.02

	V1	Central	V2	V2 stem	Docket N Attorney	Applicant Application For
8.22.2 Reactive	active				o.	on No.
SF162	HCTNLKNATNTKSSNWKEMDR SEO TO NO. 10	GEIKNCSF	KVTTSIRNKM <u>OKEYALFYK</u> LDVVPIDNDNTS	YKLINC	ABX-PHI Stanley I	Not yet a USE OF ANTIBO
CASEA2B	NCIDLRNATNATSNSNTTNTTSSSGGLMMEQ	GEIKNCSF	NITTSIRDKV <u>QKEYALFYK</u> LDIVPIDNPKNSTN	YRLISC		TRANSGE
JR-FL	NCVKDVNATNTTNDSEGTMER	GEIKNCSF	NITTSIRDEV <u>OKEYALFYK</u> LDVVPIDNNNTS	YRLISC		NIC MICE
BaL	SEQ ID NO: 20 NCTDLRNATNGNDTNTTSSSRGMVGG SEQ ID NO: 21	GEMKNCSF	NITTNIRGKV <u>OKEYALFYK</u> LDIAPIDNNSNNR	YRLISC	Reg. No.	Confirmation Filed FOR THE EFFI LIZING ACTIVIT
8.22.2 No	8.22.2 Nonreactive				/11	CIENT ISOL
HXB2d	KCTDLKNDTNTNSSSGRMIMEK	GEIKNCSF	NISTSIRGKVQKEYAFFYKLDIIPIDNDTTS	YKLTSC	43,753	ATION OF
MN-ST	NCTDLRNTTNTNNSTANNNSNSEGTIKG	GEMKNCSF	NITTSIRDKMQKEYALLYKLDIVSINDSTS	YRLISC		ntly herewit
SF2	SECTIONS: 23 NCTDLGKATNTNSSNWKEEIK SECTIONS: 24	GEIKNCSF	NITTSIRDKIQKENALFRNLDVVPIDNASTTTNYTN	YRLIHC	Tel:	MAN MONOC
					(212)-596	et 11 of 1° LONAL VEL HIV-
		FIG. 10		_	-9000	